ORIGINAL CONTRIBUTION

Vitamin E and Beta Carotene Supplementation in High Risk for Stroke

A Subgroup Analysis of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study

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Context: High serum or dietary levels of vitamin E and beta carotene appear to be associated with lower risk of stroke, but studies regarding their supplementation have not supported their use in stroke prevention.

Objective: To determine if vitamin E (*dl*-alpha tocopherol) and beta carotene supplementations could be used in prevention of stroke in men at high risk for hemorrhagic or ischemic events.

Design: Population-based, randomized, double-blind, placebo-controlled, 2 × 2 factorial design trial (the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study), conducted from April 1985 through April 30, 1993, with median follow-up of 6 years.

Interventions: Alpha tocopherol, 50 mg; beta carotene, 20 mg; both; or placebo.

Participants: From the total male population aged 50 through 69 years in southwestern Finland (n = 290 406), 29 133 male smokers were randomized to 1 of 4 treatment regimens. We excluded 614 men because of previous stroke at baseline, leaving 28 519.

Main Outcome Measures: Incident and fatal subarachnoid and intracerebral hemorrhage, cerebral infarction, and unspecified stroke.

Results: Stroke occurred in a total of 1057 men: 85 had subarachnoid and 112 had intracerebral hemorrhage, 807 had cerebral infarction, and 53 had unspecified stroke. Within 90 days from onset, 160 men died of stroke. Vitamin E supplementation increased the risk of subarachnoid hemorrhage (relative risk [RR], 2.45; 95% confidence interval [CI], 1.08-5.55) and decreased risk of cerebral infarction (RR, 0.70; 95% CI, 0.55-0.89) in hypertensive men but had no effect among normotensive men. Furthermore, it decreased the risk of cerebral infarction, without elevating the risk of subarachnoid hemorrhage, among hypertensive men with concurrent diabetes (RR, 0.33; 95% CI, 0.14-0.78). Beta carotene supplementation appeared to increase the risk of intracerebral hemorrhage and modestly decrease that of cerebral infarction among men with greater alcohol consumption.

Conclusion: Vitamin E supplementation may prevent ischemic stroke in high-risk hypertensive patients, but further studies are needed.

Arch Neurol. 2000;57:1503-1509

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VITAMIN E and beta carotene may act as antioxidants against atherosclerosis and thus prevent cerebrovascular diseases.[1,2] Besides the antioxidant effects, vitamin E and its metabolites have antiplatelet and anticlotting actions,[3-6] but the clinical importance of these actions is obscure. In our controlled trial on male smokers, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, vitamin E (*dl*-alpha tocopherol) supplementation increased the incidence and mortality due to subarachnoid hemorrhage but decreased the incidence of cerebral infarction, whereas beta carotene supplementation increased the incidence of intracerebral hemorrhage.[7]

Our aim was to examine whether there were subgroups that benefited from supplementation with vitamin E or beta carotene without an increased risk for bleeding. For this, we analyzed the effect modification of age, systolic blood pressure, serum total and high-density lipoprotein (HDL) cholesterol levels, histories of diabetes and heart disease, number of cigarettes smoked daily, alcohol consumption, and physical activity on the effects of vitamin E supplementation on subarachnoid hemorrhage and cerebral infarction, and that of beta carotene supplementation on intracerebral hemorrhage and cerebral infarction in the ATBC Study.

METHODS AND SUBJECTS

The ATBC Study had a randomized, double-blind, placebo-controlled, 2 × 2 factorial design to test the hypothesis that vitamin E and beta carotene supplements reduce the incidence of lung cancer.[8,9] From April 1985 through June 1988, 29 133 smokers (smoked ≥5 cigarettes per day) from the total male population aged 50 to 69 years in southwestern Finland (n = 290 406) were recruited and randomized to 1 of 4 treatment regimens: vitamin E, 50 mg/d; beta carotene, 20 mg/d; both; or placebo (**Figure**). All participants gave written informed consent. The study was approved by the institutional review boards of the National Public Health Institute, Helsinki, Finland, and the National Cancer Institute, Bethesda, Md, and the safety of the participants was monitored by an outside committee. Compliance was determined from the number of supplied and returned capsules and was calculated by dividing the total number of unreturned capsules by the sum of days between visits. The estimated overall compliance was 93%, with no differences between the randomization groups, and only 4% were less than 50% compliant. The dropout rate (including deaths) was 30%, and 21% of participants stopped smoking during the study. The proportions of men who dropped out or stopped smoking were evenly distributed across the trial groups.

We excluded 614 men because of history of stroke at baseline, leaving 28 519 men for the study of primary stroke. The excluded men were distributed evenly across the trial groups (166 received vitamin E; 154, beta carotene; 160, both; and 134, placebo). The median length of the follow-up, with a control visit 3 times a year, was 6.0 years, totaling 164 225 person-years. No participants were lost to follow-up.

At baseline, participants completed a questionnaire about their general background and smoking and medical histories, including a question about physician-diagnosed stroke. Alcohol consumption during the past 12 months was assessed by means of a detailed dietary history questionnaire.[10] Blood pressure was measured by nurses who were specifically trained to measure it in a standard way. Height and weight were measured. A blood sample was drawn and serum was deep-frozen at −70°C. Levels of vitamin E and beta carotene were determined by means of high-performance liquid chromatography.[11] Serum total and HDL cholesterol levels were determined enzymatically (CHOD-PAP method; Boehringer Mannheim, Mannheim, Germany). Levels of HDL cholesterol were measured after precipitation of very-low-density lipoprotein and low-density lipoprotein with dextran sulfate and magnesium chloride.

Study end points were incident subarachnoid and intracerebral hemorrhage, cerebral infarction, and unspecified stroke. Strokes were identified by record linkage to the National Hospital Discharge Register and the National Register of Causes of Death, both of which used the *International Classification of Diseases, Eighth Revision (ICD-8)*[12] until the end of 1986, then the ninth revision *(ICD-9)*.[13] The *ICD* codes 430 through 434 and 436 were included in our study, except *ICD-8* codes 431.01 and 431.91 and *ICD-9* code 432, denoting subdural hematoma, and *ICD-9* codes 4330X, 4331X, 4339X, and 4349X, denoting occlusion or stenosis of a precerebral or cerebral artery without infarction. A man was considered to have died of stroke if he died within 90 days of the onset and if stroke was the underlying cause on the death certificate. In a reviewed sample, the diagnoses of subarachnoid and intracerebral hemorrhage and cerebral infarction were reliable, according to strict standard criteria, in 79%, 82%, and 90% of the discharge diagnoses, respectively, and in 95%, 91%, and 92% of the causes of death, respectively.[14]

The baseline age was categorized as 50 to 54, 55 to 59, and at least 60 years. Systolic blood pressure was categorized as no greater than 139, 140 to 159, and at least 160 mm Hg. Serum total cholesterol level was classified as no greater than 4.9, 5.0 to 5.9, 6.0 to 6.9, and at least 7.0 mmol/L (≤192, 193-231, 232-270, and ≥271 mg/dL); and HDL cholesterol, no greater than 0.84, 0.85 to 1.14, 1.15 to 1.44, and at least 1.45 mmol/L (≤32, 33-44, 45-56, and ≥57 mg/dL). Diabetes and heart disease (coronary heart disease, myocardial infarction, valvular disease, arrhythmia, cardiac enlargement, and congestive heart failure) were based on the self-reported medical history at baseline. Smoking was determined as number of cigarettes smoked per day, and men were classified as smoking 5 to 15, 16 to 20, and at least 21 cigarettes per day. Men were classified as nondrinkers or light (≤24.0 g/d), moderate (24.1-60.0 g/d), or heavy (>60.0 g/d) drinkers. When examining drinkers only, participants were divided into tertiles of daily alcohol consumption. The level of education was categorized as primary school (<7 years), secondary school (7-12 years), or university or other higher education (>12 years). Leisure-time physical activity was categorized as sedentary or active (strenuous exercise at least once a week).

We presumed that vitamin E might be beneficial in men at low risk for subarachnoid hemorrhage but high risk for cerebral infarction. To examine this, taking into consideration the overall load of risk factors and not merely the effect of each risk factor individually, men were classified into the following 4 categories of specific stroke risk at baseline: low risk of subarachnoid hemorrhage and cerebral infarction; medium to high risk of subarachnoid hemorrhage and low risk of cerebral infarction; low risk of subarachnoid hemorrhage and medium to high risk of cerebral infarction; and medium to high risk of both. Categories were derived by calculating separately a subarachnoid hemorrhage risk score and and a cerebral

RESULTS

Stroke occurred in a total of 1057 previously stroke-free men: 85 had subarachnoid and 112 intracerebral hemorrhage, 807 had cerebral infarction, and 53 had unspecified stroke. In 90 days from onset, 160 men died of stroke, 38 due to subarachnoid and 50 due to intracerebral hemorrhage, 65 due to cerebral infarction, and 7 due to unspecified stroke. The adjusted relative risks by risk factors and stroke subtypes are shown in **Table 1**.

VITAMIN E SUPPLEMENTATION

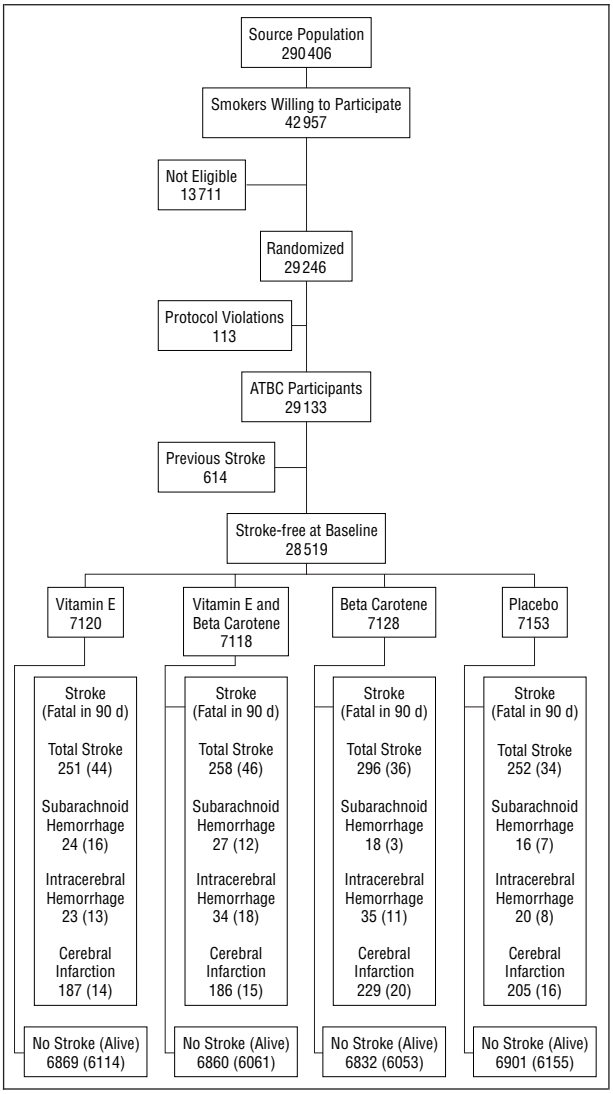
Only systolic blood pressure, of all the risk factors presented in Table 1, modified the effect of vitamin E supplementation, and therefore only those results are presented herein. Vitamin E supplementation had no effect

infarction risk score for each man. These scores were the partial logarithms of risk estimates for subarachnoid hemorrhage and cerebral infarction using the parameter estimates for age, systolic blood pressure, serum total and HDL cholesterol levels, histories of diabetes and heart disease, number of cigarettes smoked daily, alcohol consumption, and physical activity—all well-known or potentially important risk factors for stroke—from specific Cox regression models with additional adjustment for body mass index, education, and trial supplementation. Men were then divided into tertiles of subarachnoid hemorrhage and cerebral infarction risk scores, and the tertiles were cross-tabulated. Men with lowest risk scores formed the reference group, and men with risk scores in the 2 uppermost tertiles of both risks formed the medium- to high-risk group.

The statistical analyses were performed according to the intention-to-treat principle. When calculating person-years for incidence rates, the follow-up ended at any end point of interest, at death, or on April 30, 1993, the end of the trial; for mortality rates, the follow-up ended at 90 days after the specific nonfatal stroke, at death, or at the end of the trial. Unspecified stroke was not included in subtype analyses. The crude incidence rates were calculated per 10 000 person-years. The adjusted relative risks (RR) were computed using Cox proportional hazards models, adjusting for age, systolic blood pressure, serum total and HDL cholesterol levels, histories of diabetes and heart disease, number of cigarettes smoked per day, alcohol consumption, physical activity, body mass index (calculated as weight divided in kilograms by the square of height in meters), education, and vitamin E and beta carotene supplementation. The first-order interaction between vitamin E and beta carotene supplementation and age, systolic blood pressure, serum total and HDL cholesterol levels, histories of diabetes and heart disease, smoking, alcohol consumption, and physical activity was evaluated by means of stratified multivariate-adjusted Cox models and by comparing multivariate-adjusted Cox models with and without the specific interaction terms formed by vitamin E or beta carotene supplementation with each risk factor. The second-order interactions between vitamin E, systolic blood pressure, and each other risk factor mentioned above were evaluated similarly.

Five men had missing baseline values for blood pressure, 33 for serum total cholesterol level, 37 for serum HDL cholesterol level, 1963 for alcohol consumption, and 12 for physical activity. They were excluded from the multivariate analyses specifically examining the variable in question. Otherwise, missing values for covariates were replaced with group-specific means (ie, missing values of men with stroke were replaced with their average values).

on the risks of subarachnoid hemorrhage and cerebral infarction in normotensive men (systolic blood pressure, <160 mm Hg), but it increased 2.45-fold ($P=.03$) the risk of incident and 5.38-fold ($P=.03$) that of fatal subarachnoid hemorrhage; it decreased 0.70-fold ($P=.004$) the risk for incident and 0.55-fold ($P=.18$) that for fatal cerebral infarction in hypertensive men (**Table 2**). The effect modification was statistically significant only in cerebral infarction ($P=.006$). The results were similar if diastolic blood pressure was used instead of systolic blood pressure.



Recruitment, randomization, follow-up, and end points. Data are given as number of participants. ATBC indicates Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.

Further evaluation in hypertensive men only showed that vitamin E supplementation significantly decreased the risk of cerebral infarction (RR, 0.33; 95% confidence interval [CI], 0.14-0.78) without increasing the risk of subarachnoid hemorrhage in men with diabetes (**Table 3**). This effect modification by diabetes in hypertensive men was statistically significant ($P=.04$), although numbers were small. Similarly, vitamin E supplementation in hypertensive men with heart disease seemed to decrease the incidence of cerebral infarction without increasing the risk of subarachnoid hemorrhage. There was no evidence of other risk factors modifying the effect of vitamin E in hypertensive men.

VITAMIN E AND HIGH RISK FOR STROKE

The adjusted RRs for incident and fatal subarachnoid hemorrhage and cerebral infarction by baseline stroke risk level are shown in **Table 4**. The RRs for incident and fatal sub-

Table 1. Adjusted Relative Risks of Stroke Subtypes by High-Risk Factors at Baseline in 26 508 Men*

Risk Factor	Subarachnoid Hemorrhage (n = 83) RR (95% CI)	*P*	Intracerebral Hemorrhage (n = 95) RR (95% CI)	*P*	Cerebral Infarction (n = 732) RR (95% CI)	*P*
Age ≥60 y	1.03 (0.64-1.65)	.92	2.31 (1.52-3.51)	<.001	1.90 (1.64-2.21)	<.001
SBP ≥160 mm Hg	2.27 (1.43-3.61)	<.001	2.32 (1.52-3.53)	<.001	1.94 (1.66-2.27)	<.001
TC level ≥7.0 mmol/L (≥271 mg/dL)	0.91 (0.55-1.52)	.73	0.33 (0.16-0.65)	.001	1.24 (1.05-1.46)	.01
HDLC level <0.85 mmol/L (<33 mg/dL)	1.85 (1.02-3.35)	.04	0.62 (0.28-1.35)	.23	1.41 (1.15-1.73)	.001
Diabetes	0.49 (0.12-2.03)	.33	1.35 (0.58-3.14)	.48	2.24 (1.75-2.86)	<.001
Heart disease	1.05 (0.64-1.74)	.84	1.23 (0.79-1.91)	.37	1.75 (1.50-2.03)	<.001
Smoking ≥21 cigarettes per day	1.36 (0.86-2.13)	.19	1.08 (0.70-1.67)	.74	1.04 (0.89-1.22)	.60
Alcohol intake >60 g/d	1.57 (0.67-3.65)	.30	1.79 (0.86-3.75)	.12	1.48 (1.10-1.99)	.01
Sedentary lifestyle	0.80 (0.51-1.25)	.33	1.24 (0.83-1.87)	.29	1.36 (1.17-1.57)	<.001

**RR indicates relative risk; CI, confidence interval; SBP, systolic blood pressure; TC, serum total cholesterol; and HDLC, serum high-density lipoprotein cholesterol. Additionally adjusted for body mass index, education, vitamin E and beta carotene supplementation. Men with missing values for SBP, TC, HDLC levels, alcohol consumption, and physical activity were excluded.*

Table 2. Crude Incidence and Mortality per 10 000 Person-years and Relative Risks After Long-term Vitamin E Supplementation by Stroke Subtype and Systolic Blood Pressure in 28 515 Men*

Stroke Subtype and SBP, mm Hg	Vitamin E vs No Vitamin E: No. of Participants	Incidence	RR (95% CI)	Vitamin E vs No Vitamin E: No. of Participants	Mortality†	RR (95% CI)
Subarachnoid hemorrhage						
≤139	21	2.7	1.08 (0.46-2.55)	10	1.3	2.29 (0.59-8.87)
140-159	36	6.5	1.31 (0.68-2.52)	15	2.7	2.09 (0.71-6.12)
≥160	28	9.4	2.45 (1.08-5.55)	13	4.3	5.38 (1.19-24.28)
Test for interaction, *P*			.17			.41
Cerebral infarction						
≤139	243	30.8	1.15 (0.89-1.48)	22	2.8	0.82 (0.35-1.90)
140-159	292	52.7	0.82 (0.65-1.03)	21	3.8	1.15 (0.49-2.72)
≥160	272	91.2	0.70 (0.55-0.89)	22	7.4	0.55 (0.23-1.32)
Test for interaction, *P*			.006			.20

**Explanation of the abbreviations is given in the footnote to Table 1. Men with missing values for SBP were excluded.*
†Mortality within 90 days of onset.

arachnoid hemorrhage and cerebral infarction in men receiving vs those not receiving vitamin E by stroke risk level are shown in **Table 5**. The classification based on baseline risk scores identified well men with high stroke risk but contrary to what was assumed, vitamin E supplementation had no beneficial effect in men at low risk of subarachnoid hemorrhage but medium to high risk of cerebral infarction. The effect of vitamin E was seen in men with high risk for both stroke subtypes, which is in accord with 94% of hypertensive men belonging to that category.

BETA CAROTENE SUPPLEMENTATION

The effect of beta carotene supplementation was significantly modified only by alcohol consumption; the other factors did not have any consistent effect on beta carotene. Beta carotene supplementation had no effect on the risks of intracerebral hemorrhage and cerebral infarction in nondrinkers, but, with increasing alcohol consumption, it seemed to increase the risk of intracerebral hemorrhage and decrease that of cerebral infarction (**Table 6**). The effect modification was marginally nonsignificant in intracerebral hemorrhage ($P=.10$) and significant in cerebral infarction ($P=.02$). The results were similar when evaluated in drinkers only.

Multivariate adjustment did not have any material effect on the supplementation effects, therefore the crude risks (vitamin E vs no vitamin E and beta carotene vs no beta carotene) are reported.

COMMENT

In a previous report,[7] we showed that vitamin E supplementation increased the incidence of subarachnoid hemorrhage and the risk of fatal hemorrhagic strokes, and that beta carotene increased the incidence of intracerebral hemorrhage. In the present study, we analyzed the effects of vitamin E and beta carotene supplementation in relation to baseline age, systolic blood pressure, serum total and HDL cholesterol levels, histories of diabetes and heart disease, cigarette smoking, alcohol consumption, and physical activity and in connection with high risk for specific stroke.

We assumed that men at low risk of subarachnoid hemorrhage but high risk of ischemic stroke could benefit from vitamin E supplementation, without increase

Table 3. Crude Relative Risks of Long-term Vitamin E vs No Vitamin E Supplementation on Stroke Incidence and Mortality by High-Risk Factor and Stroke Subtype in Hypertensive Men*

Risk Factor	No. of Participants	Subarachnoid Hemorrhage		Cerebral Infarction	
		No. of Incident Cases (RR)	No. of Fatal Cases† (RR)	No. of Incident Cases (RR)	No. of Fatal Cases† (RR)
Diabetes	315	1 (NA) [0/1]	1 (NA) [0/1]	26 (0.33)‡	2 (NA) [0/2]
No diabetes	5086	27 (2.81)‡	12 (10.8)‡	246 (0.75)‡	20 (0.64)
Test for interaction, *P*		.99	.99	.04	.99
Heart disease	1420	8 (0.97)	4 (0.97)	98 (0.76)	10 (0.59)
No heart disease	3981	20 (3.93)‡	9 (NA) [9/0]	174 (0.67)§	12 (0.49)
Test for interaction, *P*		.11	.99	.59	.80
Other high risk factor(s) in addition to hypertension‖	2348	10 (3.96)¶	7 (5.93)¶	153 (0.60)§	11 (0.37)
No other high risk factor(s)	2657	18 (1.98)	6 (4.93)	91 (0.80)	8 (0.59)

**Hypertensive men were defined as having SBP ≥160 mm Hg. NA indicates not applicable; other abbreviations are given in the footnote to Table 1. Numbers in brackets after NA indicate participants receiving/not receiving vitamin E.*

†Indicates fatal within 90 days of onset.

‡P<.05.

§P<.01.

‖Other high-risk factors include the following: age ≥60 years, TC level ≥7.0 mmol/L (≥271 mg/dL), HDLC level <0.85 mmol/L (<33 mg/dL), diabetes, heart disease, smoking ≥21 cigarettes per day, and alcohol consumption >60g/d. Men with missing values for serum total and HDLC levels, alcohol consumption, and physical activity were excluded.

¶P<.10.

Table 4. Crude Incidence and Mortality per 10 000 Person-years and Adjusted Relative Risks of Subarachnoid Hemorrhage and Cerebral Infarction by Stroke Risk Level in 26 508 Men*

Stroke Subtype and Specific Risk Level	No. of Participants	No. of Cases	Crude Incidence	Adjusted RR (95% CI)†	No. of Cases	Crude Mortality‡	Adjusted RR (95% CI)†
SAH							
Low-risk SAH and low-risk CIR	4114	3	1.2	1.00	2	0.8	1.00
Medium- to high-risk SAH and low-risk CIR	4705	17	6.1	5.08 (1.48-17.40)	7	2.5	3.14 (0.65-15.21)
Low-risk SAH and medium- to high-risk CIR	4705	4	1.5	1.20 (0.27-5.36)	1	0.4	0.46 (0.04-5.13)
Medium- to high-risk SAH and medium- to high-risk CIR	12 984	59	8.0	6.63 (2.06-21.31)	27	3.7	4.77 (1.12-20.33)
CIR							
Low-risk SAH and low-risk CIR	4114	35	14.3	1.00	0	0.0	1.00
Medium- to high-risk SAH and low-risk CIR	4705	55	19.6	1.35 (0.88-2.07)	4	1.4	NA
Low-risk SAH and medium- to high-risk CIR	4705	154	57.3	3.99 (2.76-5.76)	17	6.3	NA
Medium- to high-risk SAH and medium- to high-risk CIR	12 984	488	66.2	4.54 (3.21-6.42)	34	4.6	NA

**SAH indicates subarachnoid hemorrhage; CIR, cerebral infarction; and NA, not applicable. Explanation of the other abbreviations is given in the footnote to Table 1. Low risk refers to the lowest tertile of risk; medium to high risk, to the 2 uppermost tertiles of risk. Men with missing values for systolic blood pressure, serum total and HDLC levels, alcohol consumption, and physical activity were excluded.*

†Adjusted for body mass index, education, and supplementation with vitamin E or beta carotene.

‡Indicates mortality within 90 days from onset.

in the number of fatal strokes. It seems, however, that men potentially benefiting from vitamin E supplementation also have high risk of both of these stroke types. This is explained by the fact that the effect of vitamin E—an increased risk of subarachnoid hemorrhage and a decreased risk of cerebral infarction—was seen mainly in hypertensive men, and that almost all hypertensive men were among those having high risk for both stroke types, reflecting the importance of blood pressure as a risk factor for any subtype of stroke. Nevertheless, hypertensive men with histories of diabetes and heart disease seemed to benefit from vitamin E supplementation. These men are also likely users of aspirin, and the possible synergistic effects of vitamin E and aspirin[15,16] could explain the effects seen in this study. Unfortunately, we had no means to evaluate the interaction between vitamin E and aspirin.

Beta carotene supplementation increased the risk of intracerebral hemorrhage and decreased that of cerebral infarction in moderate to heavy drinkers but had no effect on the respective risks in nondrinkers. We had no information on the past drinking behavior of the men, and nondrinkers most likely included lifetime teetotalers and former drinkers. Analyses excluding nondrinkers, however, gave similar results. An explanation for this could be that the effects of beta carotene and alcohol on stroke risk were connected to atherosclerotic process via lipid metabolism. Beta carotene does not seem to have any interaction with blood pressure and is not known to have any anticoagulant or antiplatelet activity, but beta carotene is carried in the lipid compartment of blood and accumulates in atherosclerotic plaques.[17,18] Nevertheless, a random finding cannot be excluded. Should beta caro-

Table 5. Crude Relative Risks After Long-term Vitamin E Supplementation by Stroke Subtype and Specific Risk Level in 26 508 Men*

Stroke Subtype and Specific Risk Level	No. of Participants	Vitamin E vs No Vitamin E		Vitamin E vs No Vitamin E	
		No. of Incident Cases	RR (95% CI)	No. of Fatal Cases†	RR (95% CI)
SAH					
Low-risk SAH and low-risk CIR	4114	3	NA (0/3)	2	NA (0/2)
Medium- to high-risk SAH and low-risk CIR	4705	17	2.42 (0.85-6.88)	7	6.07 (0.73-50.43)
Low-risk SAH and medium- to high-risk CIR	4705	4	0.99 (0.14-7.00)	1	NA (0/1)
Medium- to high-risk SAH and medium- to high-risk CIR	12 984	59	1.56 (0.92-2.63)	27	3.49 (1.41-8.64)
CIR					
Low-risk SAH and low-risk CIR	4114	35	1.58 (0.80-3.11)	0	NA (0/0)
Medium- to high-risk SAH and low-risk CIR	4705	55	0.84 (0.49-1.43)	4	1.01 (0.14-7.18)
Low-risk SAH and medium- to high-risk CIR	4705	154	1.11 (0.81-1.53)	17	0.86 (0.33-2.23)
Medium- to high-risk SAH and medium- to high-risk CIR	12 984	488	0.73 (0.61-0.87)	34	0.61 (0.31-1.22)

*Explanation of the abbreviations is given in the footnote to Table 1 and the first footnote to Table 4. Low risk refers to the lowest tertile of risk and medium to high risk to the 2 uppermost tertiles of risk. Numbers in parentheses after NA are the numbers of participants receiving/not receiving vitamin E. Men with missing values for systolic blood pressure, serum total and HDLC levels, alcohol consumption, and physical activity were excluded.

†Fatal within 90 days of onset.

Table 6. Crude Incidence per 10 000 Person-years and Relative Risks After Long-term Beta Carotene Supplementation by Stroke Subtype and Alcohol Consumption in 26 556 Men*

Alcohol Consumption by Stroke Subtype	All Men: Beta Carotene vs No Beta Carotene			Alcohol Consumption, g/d	Drinkers Only: Beta Carotene vs No Beta Carotene		
	No. of Participants	Crude Incidence	RR (95%CI)		No. of Participants	Crude Incidence	RR (95% CI)
ICH							
None	14	8.4	0.96 (0.34-2.73)	. . .	. . .	. . .	. . .
Light	58	6.2	1.33 (0.79-2.24)	≤7.3	34	7.5	1.16 (0.59-2.27)
Moderate	15	4.2	2.83 (0.90-8.88)	7.4-22.8	22	5.0	1.73 (0.72-4.12)
Heavy	8	11.2	3.16 (0.64-15.64)	≥22.9	25	5.3	2.66 (1.11-6.37)
Test for interaction, *P*			.10				.14
CIR							
None	92	55.3	1.00 (0.66-1.50)	. . .	. . .	. . .	. . .
Light	410	43.6	1.17 (0.96-1.42)	≤7.3	200	44.1	1.31 (0.99-1.73)
Moderate	183	51.6	1.00 (0.75-1.33)	7.4-22.8	187	42.7	1.07 (0.80-1.42)
Heavy	48	67.2	0.82 (0.46-1.45)	≥22.9	254	53.4	0.96 (0.75-1.23)
Test for interaction, *P*			.02				.02

*ICH indicates intracerebral hemorrhage. Explanation of the other abbreviations is given in the footnote to Table 1 and the first footnote to Table 4. Men with missing values for alcohol consumption were excluded.

tene interact with alcohol, the exact mechanism remains to be discovered.

The ATBC Study examined primarily the effect of vitamin E and beta carotene in prevention of lung and other cancers and, secondarily, cardiovascular diseases, including stroke. The randomization successfully yielded trial groups with an even distribution of baseline characteristics, including blood pressure, serum cholesterol levels, smoking, and alcohol consumption, and the compliance of the participants was good. The dropout rate, including deaths, was about 30% and similar in all randomization groups. Follow-up was complete and end-point assessment was reliable. A source of potential bias in our study was the mutually exclusive definition of the stroke end points. However, we estimated it to be negligible, even with higher incidence rates than observed in this study. Only 7% of the study population did not have data regarding baseline alcohol consumption, but with missing data more likely among heavier drinkers, there is the potential for bias with regard to the alcohol risk estimates. Nevertheless, this potential source of bias will not have altered our findings for supplementation effects or conclusions derived from them.

Our results are based on post hoc, first- and second-order interaction analyses derived from current hypotheses concerning stroke pathogenesis, but which were not specified at the start of the trial. The first-order interaction analyses were restricted to men without previous stroke at baseline, and the second-order ones, to subgroups based on hypertension. We chose to examine only the effect modification on vitamin E and beta carotene supplementation by well-established or suspected risk factors for stroke, instead of using a more rigorous statistical approach of sequential building of multivariate regression models starting with all available baseline

variables. Therefore, our findings should serve merely as an impetus for further research, and they need to be verified in future studies, especially considering that the number of statistical comparisons within the numerous subgroups elevates the possibility that some of our observations are due to chance. Three issues in particular need of further examination are the effects of vitamin E supplementation in men with hypertension and diabetes or ischemic heart disease, the possible interaction and synergistic effects of vitamin E and aspirin, and alcohol as an effect modifier of beta carotene.

CONCLUSIONS

The effects of vitamin E supplementation on stroke risks were mainly seen in hypertensive men, whereas the effects of beta carotene supplementation were seen in heavy drinkers. Vitamin E supplementation may prevent stroke in hypertensive patients at high risk of ischemic stroke, which remains to be verified in future studies.

Accepted for publication March 13, 2000.

This study was supported by contract N01-CN-45165 from the National Cancer Institute, Bethesda, Md.

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